EXHIBIT G

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Tapas Mukhopadhyay, *et al.*

Serial No.: 10/043,877

Filed: January 9, 2002

For: ANTIHELMINTHIC DRUGS AS A TREATMENT FOR HYPERPROLIFERATIVE DISEASES

Group Art Unit: 1642

Examiner: B. J. Fetterolf

Atty. Dkt. No.: INRP:095US

DECLARATION OF TAPAS MUKHOPADHYAY, SUNIL CHADA, ABNER MHASHILKAR, AND JACK A. ROTH UNDER 37 C.F.R. §1.131

We, Tapas Mukhopadhyay, Sunil Chada, Abner Mhashilkar, and Jack A. Roth, hereby declare as follows:

1. We are the joint inventors of the subject matter claimed in the above-referenced patent application, U.S.S.N. 10/043,887, filed January 9, 2002.

2. We are submitting this declaration to set forth facts demonstrating that the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to January 14, 2000, the PCT filing date of Davis (WO00/41669).

3. Attached as Exhibit 1 is Davis (WO00/41669).

4. Submitted as Exhibit 2 to this declaration is a copy of a draft manuscript of our experiments and results, entitled "Potent Induction of Apoptosis by Anthelmintics in Human Lung Cancer Cells: Involvement of Wild-Type p53 and p21 Kinase Inhibitor," which was prepared prior to January 14, 2000.

5. Reduction to practice is shown by a description of our experiments and results in our draft manuscript (Exhibit 2). This manuscript details our studies pertaining to the effect of benzimidazoles, including fenbendazole and mebendazole, on the regulation of apoptosis in human lung cancer cells. See Exhibit 2, summary, page 2. We studied the *in vitro* effect of fendendazole and mebendazole on human lung cancer cell lines, and found that these drugs dramatically inhibited the growth of lung cancer cells in culture. See Exhibit 2, pages 2 and 9-10, FIG. 1. Both febendazole and mebendazole showed an apoptotic effect on H460 cancer cells. Exhibit 2, page 9-10, FIG. 1. Western blot analysis using specific antibodies against Bcl-2, Bcl-xl, Bax, RB, cdc2, Cdk2, Cyclin A, Cyclin D and p53 demonstrated that benzimidazole treatment resulted in a dose and time dependent nuclear accumulation of wild-type p53, and no alteration in levels of any of the other proteins. Exhibit 2, pages 2, 9-10, FIG. 2, FIG. 3. The kinetics of nuclear accumulation correlated with the induction of apoptotic cell death. Exhibit 2, pages 2 and 10, FIGS. 4-6.

6. The effect of benzimidazole was further assessed on a number of human cell lines. We found that only the cell lines containing the wild-type p53 were highly sensitive to growth inhibition and apoptosis after benzimidazole treatment. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. In contrast, cell lines carrying mutated p53 were less sensitive to the cytotoxic effect of the benzimidazoles. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. Restoration of wild-type p53 function made tumor cells more sensitive to benzimidazole-induced apoptosis. Exhibit 2, page 2 and 12-13, FIG. 8. Our findings indicated that benzimidazoles selectively induce apoptosis in human NSCLC cells, strongly suggesting that a p53 dependent mechanism contributes to the cytotoxicity of benzimidazoles in human cancer cells.

7. All work disclosed in the invention disclosure form was conducted in the United States of America.

8. Therefore, the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to January 14, 2000.

9. Furthermore, we have reviewed WO00/41669 (Davis, Exhibit 1) and the Office Action dated June 28, 2004. Davis fails to disclose the invention set forth in the referenced patent application because it fails to demonstrate a cytotoxic effect of benzimidazoles against cells of a hyperproliferative lesion, such as a tumor. Rather, Davis purports to disclose use of certain 5(6)-substituted benzimidazole-2-carbamates as agents that can damage blood vessels. However, no data demonstrating damage to vasculature is provided. Instead, Davis performed an experiment (page 13, line 1 through page 14, line 4) in CaNT tumor-bearing mice wherein the mice were injected with various compounds intraperitoneally, and then were injected with a fluorescent dye 6 or 24 hr later. One minute later, the animals were killed and tumors evaluated under UV illumination. Blood vessels were identified by fluorescent outlines and vascular volume was said to be quantified using the method of Chalkley, 1943 (J. Natl. Cancer Inst., 4:47-53, 1943; Exhibit 3). However, the "quantitative morphologic tissue analysis" set forth in Chalkley was not contemplated for use in measuring vascular volume. Rather, Chalkley describes a method for evaluating ratios of nucleocytoplasmic volumes or comparing volume ratios of active versus inactive glands. Therefore, it is clear that the methods disclosed in Chalkley are not a validated surrogate assay for vascular volume, and as such, the data presented in Davis is difficult to accurately interpret.

10. Davis fails to provide evidence to indicate that the observed effect on vascular volume has any tumor-selectivity, as only tumor vasculature was evaluated. Furthermore, there

is no indication that the presumed reduction in tumor vascular volume observed in Davis (Exhibit 1, page 13, line 1 through page 14, line 4) represents vascular damage as a result of administration of a benzimidazole. Data are presented as a percent reduction compared to control. However, no information pertaining to the control is provided. It is well known that tumors possess "leaky" vasculature, and thus the reduction in UV staining is not expected, as it would be predicted that the lack of patent blood vessels in tumors would produce enhanced leakage of fluorescent dye in tumors, which may be exacerbated by benzimidazoles.

11. Although Davis claims "use of vascular damaging agents," no evidence of vascular damage is presented. Furthermore, no cytopathic effect against tumor cells was shown in Davis. A neovascular membrane that supplies blood to a tumor contains cells, such as endothelial cells, that are distinct from tumor cells served by the neovascular membrane. In particular, the cells of the neovascular membrane are not cancer cells.

12. We have previously demonstrated that Mebendazole does not kill human primary endothelial cells in culture (Mukhopadhyay *et al.*, Clin. Cancer Res. 8:2963-9, 2002; Exhibit 4). Thus, the cytotoxic effect of Mebendazole *in vivo* is directed against tumor cells and not endothelium. We have demonstrated that MZ blocks production of VEGF from tumor cells (data not shown) which can enhance anti-tumor effects – this is likely the mechanism underlying the anti-angiogenic effect, and is mediated via tumor cell activity and not directly against endothelium .

13. There exists more than one mechanism of cell death. Apoptosis is but one example. Another major mechanism of cell death is necrosis. A third mechanism is anoikis. These mechanisms of cell death are defined by morphological features of the cell. When a neovascular membrane associated with a tumor is damaged or occluded, it does not necessarily

follow that tumor cell death due to apoptosis will result. For instance, tumor cell death may be by necrosis due to lack of nutrients and oxygen.

14. Furthermore, recent clinical studies have failed to demonstrate significant patient benefit with anti-angiogenic agents, such as thalidomide and endostatin. Davis et al., (Clin. Cancer Res. 10:33-42, 2004; Exhibit 5) recently showed that endostatin can elicit anti-angiogenic effects in human tumors, however the reduced vascularization did not correlate with induction of apoptosis in tumor cells and did not result in tumor growth reduction. Similar lack of efficacy of endostatin was found in an independent study (Thomas *et al.*, J Clin Oncol. 21:223-31, 2003; Exhibit 6), and was also observed in trials with thalidomide (Thomas *et al.*, Br J Haematol. 123:436-41, 2003; Exhibit 7).

15. Expression of a tumor suppressor gene by a cell is not known to be a requirement for a cell to be a tumor cell. Some tumor cells express a tumor suppressor gene, whereas others do not. Furthermore, many tumor cells express a mutant tumor suppressor gene. It is a widely held belief that the function of tumor suppressor genes is to protect against development of cancer: thus expression of tumor suppressor genes in cancerous cells generally results in activation of cell cycle arrest mechanisms and ultimately, cell death. This concept has been exhaustively validated using the p53 tumor suppressor, however additional studies have shown the concept to be a truism. For example, it has been shown that genetic transfer of p53, Rb, E2F-1, PTEN, p16, mda-7, APC, and fus-1 results in tumor cell death. In contrast, expression of oncogenes (which promote cell proliferation and provide cell survival signals) is a requirement for tumor cell growth. Examples of such oncogenes, which act in opposition to tumor suppressors, are PI3K, bcl-2, beta-catenin, surviving, and c-myc.

16. Regarding drug resistance, not all tumor cells are multi-drug resistant. Multi-drug resistance is an acquired trait and generally requires selection with cytotoxic drugs to render a tumor cell multi-drug resistant. Tumor cells *per se* are responsive to cytotoxic drugs. However, due to their inherent property of mutability, drug-sensitive cells are killed and drug-resistant clones are selected. Furthermore, considerable polymorphism exists in expression and function of P-glycoprotein, the MDR1 gene product (see Ieiri *et al.*, Clin Pharmacokinet.43:553-76, 2004; Exhibit 8). The MDR1 (ABCB1) gene polymorphism and its clinical implications. This natural variation in MDR1 can strongly affect therapy of many diseases.

17. We hereby declare that all statements made by our own knowledge are true and all statements made on information and belief are believed to be true and further that statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment under § 100 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date	Tapas Mukhopadhyay
11/02/04 Date	Sunil Chada
Date	Abner Mhashilkar
Date	Jack A. Roth

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Tapas Mukhopadhyay, *et al.*

Serial No.: 10/043,877

Filed: January 9, 2002

For: ANTIHELMINTHIC DRUGS AS A TREATMENT FOR HYPERPROLIFERATIVE DISEASES

Group Art Unit: 1642

Examiner: B. J. Fetterolf

Atty. Dkt. No.: INRP:095US

DECLARATION OF TAPAS MUKHOPADHYAY, SUNIL CHADA, ABNER MHASHILKAR, AND JACK A. ROTH UNDER 37 C.F.R. §1.131

We, Tapas Mukhopadhyay, Sunil Chada, Abner Mhashilkar, and Jack A. Roth, hereby declare as follows:

1. We are the joint inventors of the subject matter claimed in the above-referenced patent application, U.S.S.N. 10/043,887, filed January 9, 2002.

2. We are submitting this declaration to set forth facts demonstrating that the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to January 14, 2000, the PCT filing date of Davis (WO00/41669).

3. Attached as Exhibit 1 is Davis (WO00/41669).

4. Submitted as Exhibit 2 to this declaration is a copy of a draft manuscript of our experiments and results, entitled "Potent Induction of Apoptosis by Anthelmintics in Human Lung Cancer Cells: Involvement of Wild-Type p53 and p21 Kinase Inhibitor," which was prepared prior to January 14, 2000.

5. Reduction to practice is shown by a description of our experiments and results in our draft manuscript (Exhibit 2). This manuscript details our studies pertaining to the effect of benzimidazoles, including fenbendazole and mebendazole, on the regulation of apoptosis in human lung cancer cells. See Exhibit 2, summary, page 2. We studied the *in vitro* effect of fendendazole and mebendazole on human lung cancer cell lines, and found that these drugs dramatically inhibited the growth of lung cancer cells in culture. See Exhibit 2, pages 2 and 9-10, FIG. 1. Both febendazole and mebendazole showed an apoptotic effect on H460 cancer cells. Exhibit 2, page 9-10, FIG. 1. Western blot analysis using specific antibodies against Bcl-2, Bcl-xl, Bax, RB, cdc2, Cdk2, Cyclin A, Cyclin D and p53 demonstrated that benzimidazole treatment resulted in a dose and time dependent nuclear accumulation of wild-type p53, and no alteration in levels of any of the other proteins. Exhibit 2, pages 2, 9-10, FIG. 2, FIG. 3. The kinetics of nuclear accumulation correlated with the induction of apoptotic cell death. Exhibit 2, pages 2 and 10, FIGS. 4-6.

6. The effect of benzimidazole was further assessed on a number of human cell lines. We found that only the cell lines containing the wild-type p53 were highly sensitive to growth inhibition and apoptosis after benzimidazole treatment. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. In contrast, cell lines carrying mutated p53 were less sensitive to the cytotoxic effect of the benzimidazoles. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. Restoration of wild-type p53 function made tumor cells more sensitive to benzimidazole-induced apoptosis. Exhibit 2, page 2 and 12-13, FIG. 8. Our findings indicated that benzimidazoles selectively induce apoptosis in human NSCLC cells, strongly suggesting that a p53 dependent mechanism contributes to the cytotoxicity of benzimidazoles in human cancer cells.

7. All work disclosed in the invention disclosure form was conducted in the United States of America.

8. Therefore, the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to January 14, 2000.

9. Furthermore, we have reviewed WO00/41669 (Davis, Exhibit 1) and the Office Action dated June 28, 2004. Davis fails to disclose the invention set forth in the referenced patent application because it fails to demonstrate a cytotoxic effect of benzimidazoles against cells of a hyperproliferative lesion, such as a tumor. Rather, Davis purports to disclose use of certain 5(6)-substituted benzimidazole-2-carbamates as agents that can damage blood vessels. However, no data demonstrating damage to vasculature is provided. Instead, Davis performed an experiment (page 13, line 1 through page 14, line 4) in CaNT tumor-bearing mice wherein the mice were injected with various compounds intraperitoneally, and then were injected with a fluorescent dye 6 or 24 hr later. One minute later, the animals were killed and tumors evaluated under UV illumination. Blood vessels were identified by fluorescent outlines and vascular volume was said to be quantified using the method of Chalkley, 1943 (J. Natl. Cancer Inst., 4:47-53, 1943; Exhibit 3). However, the "quantitative morphologic tissue analysis" set forth in Chalkley was not contemplated for use in measuring vascular volume. Rather, Chalkley describes a method for evaluating ratios of nucleocytoplasmic volumes or comparing volume ratios of active versus inactive glands. Therefore, it is clear that the methods disclosed in Chalkley are not a validated surrogate assay for vascular volume, and as such, the data presented in Davis is difficult to accurately interpret.

10. Davis fails to provide evidence to indicate that the observed effect on vascular volume has any tumor-selectivity, as only tumor vasculature was evaluated. Furthermore, there

is no indication that the presumed reduction in tumor vascular volume observed in Davis (Exhibit 1, page 13, line 1 through page 14, line 4) represents vascular damage as a result of administration of a benzimidazole. Data are presented as a percent reduction compared to control. However, no information pertaining to the control is provided. It is well known that tumors possess "leaky" vasculature, and thus the reduction in UV staining is not expected, as it would be predicted that the lack of patent blood vessels in tumors would produce enhanced leakage of fluorescent dye in tumors, which may be exacerbated by benzimidazoles.

11. Although Davis claims "use of vascular damaging agents," no evidence of vascular damage is presented. Furthermore, no cytopathic effect against tumor cells was shown in Davis. A neovascular membrane that supplies blood to a tumor contains cells, such as endothelial cells, that are distinct from tumor cells served by the neovascular membrane. In particular, the cells of the neovascular membrane are not cancer cells.

12. We have previously demonstrated that Mebendazole does not kill human primary endothelial cells in culture (Mukhopadhyay *et al.*, Clin. Cancer Res. 8:2963-9, 2002; Exhibit 4). Thus, the cytotoxic effect of Mebendazole *in vivo* is directed against tumor cells and not endothelium. We have demonstrated that MZ blocks production of VEGF from tumor cells (data not shown) which can enhance anti-tumor effects – this is likely the mechanism underlying the anti-angiogenic effect, and is mediated via tumor cell activity and not directly against endothelium.

13. There exists more than one mechanism of cell death. Apoptosis is but one example. Another major mechanism of cell death is necrosis. A third mechanism is anoikis. These mechanisms of cell death are defined by morphological features of the cell. When a neovascular membrane associated with a tumor is damaged or occluded, it does not necessarily

follow that tumor cell death due to apoptosis will result. For instance, tumor cell death may be by necrosis due to lack of nutrients and oxygen.

14. Furthermore, recent clinical studies have failed to demonstrate significant patient benefit with anti-angiogenic agents, such as thalidomide and endostatin. Davis et al., (Clin. Cancer Res. 10:33-42, 2004; Exhibit 5) recently showed that endostatin can elicit anti-angiogenic effects in human tumors, however the reduced vascularization did not correlate with induction of apoptosis in tumor cells and did not result in tumor growth reduction. Similar lack of efficacy of endostatin was found in an independent study (Thomas *et al.*, J Clin Oncol. 21:223-31, 2003; Exhibit 6), and was also observed in trials with thalidomide (Thomas *et al.*, Br J Haematol. 123:436-41, 2003; Exhibit 7).

15. Expression of a tumor suppressor gene by a cell is not known to be a requirement for a cell to be a tumor cell. Some tumor cells express a tumor suppressor gene, whereas others do not. Furthermore, many tumor cells express a mutant tumor suppressor gene. It is a widely held belief that the function of tumor suppressor genes is to protect against development of cancer: thus expression of tumor suppressor genes in cancerous cells generally results in activation of cell cycle arrest mechanisms and ultimately, cell death. This concept has been exhaustively validated using the p53 tumor suppressor, however additional studies have shown the concept to be a truism. For example, it has been shown that genetic transfer of p53, Rb, E2F-1, PTEN, p16, mda-7, APC, and fus-1 results in tumor cell death. In contrast, expression of oncogenes (which promote cell proliferation and provide cell survival signals) is a requirement for tumor cell growth. Examples of such oncogenes, which act in opposition to tumor suppressors, are PI3K, bcl-2, beta-catenin, surviving, and c-myc.

16. Regarding drug resistance, not all tumor cells are multi-drug resistant. Multi-drug resistance is an acquired trait and generally requires selection with cytotoxic drugs to render a tumor cell multi-drug resistant. Tumor cells *per se* are responsive to cytotoxic drugs. However, due to their inherent property of mutability, drug-sensitive cells are killed and drug-resistant clones are selected. Furthermore, considerable polymorphism exists in expression and function of P-glycoprotein, the MDR1 gene product (see Ieiri *et al.*, Clin Pharmacokinet.43:553-76, 2004; Exhibit 8). The MDR1 (ABCB1) gene polymorphism and its clinical implications. This natural variation in MDR1 can strongly affect therapy of many diseases.

17. We hereby declare that all statements made by our own knowledge are true and all statements made on information and belief are believed to be true and further that statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment under § 100 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date	Tapas Mukhopadhyay
Date	Sunil Chada
11/02/04 Date	Abner Mhashilkar
Date	Jack A. Roth

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Tapas Mukhopadhyay, *et al.*	Group Art Unit: 1642
Serial No.: 10/043,877	Examiner: B. J. Fetterolf
Filed: January 9, 2002	Atty. Dkt. No.: INRP:095US
For: ANTIHELMINTHIC DRUGS AS A TREATMENT FOR HYPERPROLIFERATIVE DISEASES	

DECLARATION OF TAPAS MUKHOPADHYAY, SUNIL CHADA, ABNER MHASHILKAR, AND JACK A. ROTH UNDER 37 C.F.R. §1.131

We, Tapas Mukhopadhyay, Sunil Chada, Abner Mhashilkar, and Jack A. Roth, hereby declare as follows:

1. We are the joint inventors of the subject matter claimed in the above-referenced patent application, U.S.S.N. 10/043,887, filed January 9, 2002.

2. We are submitting this declaration to set forth facts demonstrating that the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to January 14, 2000, the PCT filing date of Davis (WO00/41669).

3. Attached as Exhibit 1 is Davis (WO00/41669).

4. Submitted as Exhibit 2 to this declaration is a copy of a draft manuscript of our experiments and results, entitled "Potent Induction of Apoptosis by Anthelmintics in Human Lung Cancer Cells: Involvement of Wild-Type p53 and p21 Kinase Inhibitor," which was prepared prior to January 14, 2000.

5. Reduction to practice is shown by a description of our experiments and results in our draft manuscript (Exhibit 2). This manuscript details our studies pertaining to the effect of benzimidazoles, including fenbendazole and mebendazole, on the regulation of apoptosis in human lung cancer cells. See Exhibit 2, summary, page 2. We studied the *in vitro* effect of fendendazole and mebendazole on human lung cancer cell lines, and found that these drugs dramatically inhibited the growth of lung cancer cells in culture. See Exhibit 2, pages 2 and 9-10, FIG. 1. Both febendazole and mebendazole showed an apoptotic effect on H460 cancer cells. Exhibit 2, page 9-10, FIG. 1. Western blot analysis using specific antibodies against Bcl-2, Bcl-xl, Bax, RB, cdc2, Cdk2, Cyclin A, Cyclin D and p53 demonstrated that benzimidazole treatment resulted in a dose and time dependent nuclear accumulation of wild-type p53, and no alteration in levels of any of the other proteins. Exhibit 2, pages 2, 9-10, FIG. 2, FIG. 3. The kinetics of nuclear accumulation correlated with the induction of apoptotic cell death. Exhibit 2, pages 2 and 10, FIGS. 4-6.

6. The effect of benzimidazole was further assessed on a number of human cell lines. We found that only the cell lines containing the wild-type p53 were highly sensitive to growth inhibition and apoptosis after benzimidazole treatment. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. In contrast, cell lines carrying mutated p53 were less sensitive to the cytotoxic effect of the benzimidazoles. Exhibit 2, pages 2 and 11-13, FIGS. 7-8, Table I, and Table II. Restoration of wild-type p53 function made tumor cells more sensitive to benzimidazole-induced apoptosis. Exhibit 2, page 2 and 12-13, FIG. 8. Our findings indicated that benzimidazoles selectively induce apoptosis in human NSCLC cells, strongly suggesting that a p53 dependent mechanism contributes to the cytotoxicity of benzimidazoles in human cancer cells.

7. All work disclosed in the invention disclosure form was conducted in the United States of America.

8. Therefore, the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to January 14, 2000.

9. Furthermore, we have reviewed WO 0/41669 (Davis, Exhibit 1) and the Office Action dated June 28, 2004. Davis fails to disclose the invention set forth in the referenced patent application because it fails to demonstrate a cytotoxic effect of benzimidazoles against cells of a hyperproliferative lesion, such as a tumor. Rather, Davis purports to disclose use of certain 5(6)-substituted benzimidazole-2-carbamates as agents that can damage blood vessels. However, no data demonstrating damage to vasculature is provided. Instead, Davis performed an experiment (page 13, line 1 through page 14, line 4) in CaNT tumor-bearing mice wherein the mice were injected with various compounds intraperitoneally, and then were injected with a fluorescent dye 6 or 24 hr later. One minute later, the animals were killed and tumors evaluated under UV illumination. Blood vessels were identified by fluorescent outlines and vascular volume was said to be quantified using the method of Chalkley, 1943 (J. Natl. Cancer Inst., 4:47-53, 1943; Exhibit 3). However, the "quantitative morphologic tissue analysis" set forth in Chalkley was not contemplated for use in measuring vascular volume. Rather, Chalkley describes a method for evaluating ratios of nucleocytoplasmic volumes or comparing volume ratios of active versus inactive glands. Therefore, it is clear that the methods disclosed in Chalkley are not a validated surrogate assay for vascular volume, and as such, the data presented in Davis is difficult to accurately interpret.

10. Davis fails to provide evidence to indicate that the observed effect on vascular volume has any tumor-selectivity, as only tumor vasculature was evaluated. Furthermore, there

is no indication that the presumed reduction in tumor vascular volume observed in Davis (Exhibit 1, page 13, line 1 through page 14, line 4) represents vascular damage as a result of administration of a benzimidazole. Data are presented as a percent reduction compared to control. However, no information pertaining to the control is provided. It is well known that tumors possess "leaky" vasculature, and thus the reduction in UV staining is not expected, as it would be predicted that the lack of patent blood vessels in tumors would produce enhanced leakage of fluorescent dye in tumors, which may be exacerbated by benzimidazoles.

11. Although Davis claims "use of vascular damaging agents," no evidence of vascular damage is presented. Furthermore, no cytopathic effect against tumor cells was shown in Davis. A neovascular membrane that supplies blood to a tumor contains cells, such as endothelial cells, that are distinct from tumor cells served by the neovascular membrane. In particular, the cells of the neovascular membrane are not cancer cells.

12. We have previously demonstrated that Mebendazole does not kill human primary endothelial cells in culture (Mukhopadhyay *et al.*, Clin. Cancer Res. 8:2963-9, 2002; Exhibit 4). Thus, the cytotoxic effect of Mebendazole *in vivo* is directed against tumor cells and not endothelium. We have demonstrated that MZ blocks production of VEGF from tumor cells (data not shown) which can enhance anti-tumor effects – this is likely the mechanism underlying the anti-angiogenic effect, and is mediated via tumor cell activity and not directly against endothelium.

13. There exists more than one mechanism of cell death. Apoptosis is but one example. Another major mechanism of cell death is necrosis. A third mechanism is anoikis. These mechanisms of cell death are defined by morphological features of the cell. When a neovascular membrane associated with a tumor is damaged or occluded, it does not necessarily

follow that tumor cell death due to apoptosis will res ılt. For instance, tumor cell death may be by necrosis due to lack of nutrients and oxygen.

14. Furthermore, recent clinical stud es have failed to demonstrate significant patient benefit with anti-angiogenic agents, such as thalidomide and endostatin. Davis et al., (Clin. Cancer Res. 10:33-42, 2004; Exhibit 5) rece tly showed that endostatin can elicit anti-angiogenic effects in human tumors, however the re uced vascularization did not correlate with induction of apoptosis in tumor cells and did not res lt in tumor growth reduction. Similar lack of efficacy of endostatin was found in an indepe dent study (Thomas *et al.*, J Clin Oncol. 21:223-31, 2003; Exhibit 6), and was also observed n trials with thalidomide (Thomas *et al.*, Br J Haematol. 123:436-41, 2003; Exhibit 7).

15. Expression of a tumor suppressor ger e by a cell is not known to be a requirement for a cell to be a tumor cell. Some tumor cells expr ss a tumor suppressor gene, whereas others do not. Furthermore, many tumor cells express a r utant tumor suppressor gene. It is a widely held belief that the function of tumor suppressor genes is to protect against development of cancer: thus expression of tumor suppressor ger es in cancerous cells generally results in activation of cell cycle arrest mechanisms and ult mately, cell death. This concept has been exhaustively validated using the p53 tumor suppre sor, however additional studies have shown the concept to be a truism. For example, it has beer shown that genetic transfer of p53, Rb, E2F-1, PTEN, p16, mda-7, APC, and fus-1 results in umor cell death. In contrast, expression of oncogenes (which promote cell proliferation and p ovide cell survival signals) is a requirement for tumor cell growth. Examples of such onc ogenes, which act in opposition to tumor suppressors, are PI3K, bcl-2, beta-catenin, survivin , and c-myc.

16. Regarding drug resistance, not all tumor cells are multi-drug resistant. Multi-drug resistance is an acquired trait and generally requires selection with cytotoxic drugs to render a tumor cell multi-drug resistant. Tumor cells *per se* are responsive to cytotoxic drugs. However, due to their inherent property of mutability, drug-sensitive cells are killed and drug-resistant clones are selected. Furthermore, considerable polymorphism exists in expression and function of P-glycoprotein, the MDR1 gene product (see Ieiri *et al.*, Clin Pharmacokinet.43:553-76, 2004; Exhibit 8). The MDR1 (ABCB1) gene polymorphism and its clinical implications. This natural variation in MDR1 can strongly affect therapy of many diseases.

17. We hereby declare that all statements made by our own knowledge are true and all statements made on information and belief are believed to be true and further that statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment under § 100 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date	Tapas Mukhopadhyay
Date	Sunil Chada
Date	Abner Mhashilkar
11/4/04 Date	Jack A. Roth